particles, with at least one encapsulated Gd_2O_3 particle per microsphere. Preferably, each microsphere includes a plurality of particles. Further, the gadolinium oxide preferably is present in the microspheres in spherical form. The outer shell of the microsphere may comprise proteins, such as bovine serum albumin ("BSA"), human serum albumin ("HSA"), pepsin, conjugated antibodies or antibody shells; lipids, such as phospholipids, glycolipids, and cholesterol used in some liposome preparations; gelatin; and carbohydrates, such as dextrose and dextrose-albumin, and combinations thereof, or any other substance capable of imparting the characteristics of elasticity, small size, spherical shape and having a metabolic pathway, biodistribution, and subsequent elimination pharmakokinetics. Preferably, a water-in-oil emulsion polymerization method as known to those skilled in the art may be modified to prepare the GOAM.

As an example, the GOAM may be prepared by first mixing approximately 5 grams of BSA in 10 ml of distilled water and passing the solution through a 0.2 μm filter. One gram of Gd_2O_3 is added to the aqueous solution. The colloid solution includes Gd_2O_3 particles measuring between about 50 Angstroms (Å) to about 2 μm in diameter, preferably between about 50 to about 750 Å, and more preferably between about 200 to about 400 Å. The BSA and Gd_2O_3 mixture is first mixed in water and then added to approximately 40 ml of oil, such as cottonseed, canola and the like, with stirring. The mixture then is sonicated at an acoustic power of 70 watts/cm^2 using a Misonix 2020XL sonicator fitted with a microprobe tip for up to about 5 minutes. This solution is added dropwise to about 10 ml of oil preheated to between about 100°C and about 180°C, and heated to between about 100°C and about 180°C. The solution is allowed to cool to room temperature with stirring. The cooled GOAM

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solution is separated from unused starting materials via filtered centrifugation. The resulting solution is washed in either ether, ethanol, acetone, or the like, and re-suspended in buffered saline solution or distilled water. As an example, the resulting composition may have a bubble concentration of between about 10^6 to about 10^9 bubbles/ml of solution and a gadolinium concentration of about 2 to about 10 mg/l (as measured via ICP analysis).

Figure 3 illustrates microspheres having an outer protein shell surrounding a gadolinium compound. The albumin shell encapsulates particles of Gd_2O_3. Preferably, the Gd_2O_3 albumin microspheres measure between about 0.5 to about 7 μm in diameter and more preferably less than about 4 μm in diameter.

The gadolinium oxide composition of the present invention is particularly suitable for use as a contrast agent for a plurality of imaging modalities. Use of contrast agents in accordance with the present invention allows a reduced amount of gadolinium to be administered while still maintaining the image-enhancing effects of the contrast agent with MR and US imaging thereby reducing potential toxic effects associated with gadolinium.

Pegylated gadolinium oxide albumin microspheres also can be prepared from the synthesized GOAM. With pegylation, polyethylene glycol ("PEG") chains can be added to the outer shells of the microspheres. As an example, polyethylene glycol 2000 ("PEG 2000") can be attached to the GOAM using various pegylation procedures. The uptake of GOAM generally is altered, such that biodistribution of the contrast agent in soft tissues, such as the liver and spleen, changes. By surface modification of the GOAM, the half life of the contrast agent in the blood pool is increased, allowing for increased effectiveness of GOAM as a blood-pool enhancement agent.

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In another embodiment of the present invention, the individual Gd_2O_3 particles may be pegylated and may then be encapsulated, if desired. The individual Gd_2O_3 particles are stabilized with a carbohydrate polyethylene glycol coat using a modified pegylation procedure. The Gd_2O_3 particles preferably have diameters of between about 200 to about 400 Å. Using Gd_2O_3 particles in this size range that have been pegylated will provide a relatively high concentration of Gd_2O_3 and will modify the biodistribution of the contrast agent in the body.

The contrast agents of the present invention can be used with US, MR, and CT, which will allow correlative studies to be performed. When used with US, both the microsphere shell and the encapsulated particle interact with ultrasonic waves, altering the scatter and absorption characteristics and thereby providing an enhanced image. The encapsulated gadolinium compound reacts during MR to alter the magnetic field of the tissue and acts as an absorber of x-rays during CT, thereby providing enhanced images with these modalities. The images obtained by the various modalities with the contrast agents of the present invention have increased clarity and contrast.

Use of the contrast agents provides a cost-effective means of diagnosis. The contrast agents can be used with multiple modalities, certain of which are less expensive to perform and may be used as initial indicators for diagnosis. For example, imaging with US is not as costly as with MR, and US may be conducted prior to MR or other techniques to provide an initial diagnosis, such that subsequent, more costly, tests may be more focused or possibly avoided.

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